

# The Modern Age of Acne Therapy:

## A Review of Current Treatment Options

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### Abstract

This review of current acne treatments begins with the crucial discovery in 1979 of isotretinoin treatment for nodulocystic acne. This drug's approval in 1982 revolutionized therapy, since it was the first oral acne-specific drug, and it provided prolonged remissions. In addition, it may prevent the emergence of resistant bacteria, a problem linked to the traditional use of antibiotics for acne.

Patients who are not candidates for isotretinoin therapy may benefit from one of the other drugs or drug combinations reviewed, including the third-generation topical retinoids adapalene and tazarotene, retinoic acid reformulated in new vehicles, azelaic acid, and topical antibiotics. Proper selection and education of patients are essential, since serious consequences may result from poorly monitored use of antibiotics and retinoids.

**Key Words:** Acne, review, therapy, treatment, isotretinoin, retinoid, antibiotic, azelaic acid, adapalene, tazarotene, benzoyl peroxide.

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### Introduction

THE PERIOD 1945–1995 has been named the “Golden Age of Treatment” in dermatology by Thomas B. Fitzpatrick (1). These fifty years saw a great number of therapeutic discoveries, ranging from penicillin for syphilis to topical corticosteroids for psoriasis. In the field of acne treatment, the single most important event probably was the 1979 report of prolonged remissions of cystic acne attributable to 13-cis-retinoic acid (isotretinoin) (2).

In 1982, the Food and Drug Administration (FDA) approved the use of isotretinoin for treating recalcitrant nodulocystic acne. Unlike traditional antibiotic treatment, isotretinoin's sole approved indication is cystic acne. Its effect lasts months to years after a 20-week course, a claim that no other acne medication can match. Also, its use does not promote antibiotic-resistant bacteria, an important concern (3).

Since isotretinoin is reserved specifically for severe acne, it has not made other acne treatments obsolete. Yet it appears to provide an acne treatment that is comfortable, safe, effective, and lasting.

### Acne: Definition, Demographics and Pathogenesis

Acne is a chronic inflammatory condition of the pilosebaceous unit. The comedo, a plug of sebum and keratin lodged in the follicular duct, is its primary lesion. Comedones appear clinically as blackheads and whiteheads. When a closed comedo or microcomedo causes the follicular wall to rupture, an inflammatory reaction ensues, resulting in clinically evident papules, pustules, nodules and cysts. The term “cyst” is a misnomer that refers to a pus-filled acne lesion greater than 5 mm in diameter, in which the wall is composed of inflammatory cells and scar tissue.

The typical clinical picture of acne is an eruption located on the face, with the upper trunk often being affected as well. Adolescents and young adults are most often afflicted, with estimates of 85–100% of those aged 12–24 being affected, at least intermittently, during those years (4, 5). Within the adolescent group, the frequency and severity of acne, as well as its tendency toward scarring, is greater in males than in females. However, the persistence of acne into adulthood is more common in females (6).

Contrary to popular belief, hygiene plays at most a minor role in the etiology of acne, and diet appears to have little or no influence. However, true acne can be exacerbated by external factors such as friction (“acne mechan-

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ica”) (7) and pore-clogging cosmetics (“acne cosmetica”) (8). The etiology of acne lies in a confluence of several factors which together produce clinical acne. Research suggests that genetic control, along with the stimulation of androgenic hormones, is responsible for abnormal sebum secretion (9, 10). The latter, together with faulty corneocyte occlusion of the pilosebaceous orifice, produces comedonal acne (11). The anaerobic diphtheroid *Propionibacterium acnes* is believed to play a pivotal role in converting comedonal acne to inflammatory acne. Previously *P. acnes* was thought to incite inflammation by breaking down neutral sebaceous lipids into free fatty acids, but newer research favors a direct role for *P. acnes* in neutrophil attraction (12).

### Treatment of Acne

Today’s therapeutic modalities for acne are aimed at one or more of its pathogenic precipitants, which include androgenic hormonal stimulation, hypersecretion of sebum, faulty occlusion of the follicular orifice, *P. acnes* colonization, and inflammation. Combination therapy, therefore, is the usual approach, with isotretinoin treatment being the notable exception.

### Comedonal Acne

When open and closed comedones are the principal manifestations of acne, there is no substitute for the immediate results achieved with acne surgery, which is the manual extraction of impacted comedones, performed in the physician’s office. Most patients benefit by having this procedure performed at 3–6 week intervals until topical medications take effect. Patients should be discouraged from attempting this at home, due to the risk of infection and the potential for scarring due to excessive trauma to the skin.

The most effective topical medications for comedonal acne are the so-called keratolytic agents, which target faulty occlusion of the follicular orifice. This group includes the retinoids, azelaic acid, and the alpha-hydroxy acids (AHAs).

### Retinoids

Topical Vitamin A acid (tretinoin, all-trans-retinoic acid) and its synthetic analogs, termed retinoids, comprise the most potent group of currently available keratolytic agents. Medica-

tions in this group include topical tretinoin, adapalene and tazarotene, as well as oral isotretinoin. Considerable current research is focused on this category.

Tretinoin preceded the others in this class by a decade or more, becoming available as a topical acne treatment in the United States in 1971. Tretinoin exerts its effects by increasing the turnover of follicular epithelial cells, thus normalizing keratinization (13). This leads to the extrusion of comedones and also accelerates corneocyte shedding, thereby inhibiting comedo formation (14).

Early formulations of tretinoin tended to cause excessive skin irritation, due to the high concentration of the active ingredient in a penetrating hydroalcoholic vehicle. Now available are a number of formulations which utilize a lower tretinoin concentration (0.025%) and cream vehicles which are designed to be more emollient and less penetrating. Two of the newest topical tretinoin products are based on slow-release delivery systems (15). One of these contains tretinoin (0.025%) in a gel or cream base containing polyolprepolymer-2, a large-polymer compound that delays absorption of the active ingredient into epidermal cells. The second formulation designed to slow delivery is a tretinoin (0.1%) gel, in which the active ingredient is incorporated into microsponges, which are macroporous beads 10–25 microns in diameter.

Despite these improvements, the use of tretinoin in dermatology practice is often limited by local skin irritation. In addition, the onset of improvement is relatively delayed and variable — one to three months is common (16). Some patients experience clinical worsening after 2–4 weeks of treatment (17), when the extrusion of comedones can elicit a pustular reaction. Tretinoin also increases sun sensitivity, necessitating regular sunblock use.

Two recently developed topical polyaromatic retinoids, adapalene and tazarotene, may provide therapeutic advantages over tretinoin. These new agents have molecular configurations that are selective for nuclear retinoic acid receptors. It is theorized that these receptors, when activated, affect keratinocyte differentiation and block inflammation (17–19).

Adapalene is a synthetic naphthoic acid derivative. Its mechanism of action is twofold: first, it inhibits comedo formation through its ability to bind to retinoic acid receptors and modulate cell differentiation; and second, it possesses direct anti-inflammatory activity

(20). Adapalene is available in gel, solution and cream formulations containing 0.1% active agent.

In a multicenter study of more than 300 patients, adapalene (0.1% gel) was compared to tretinoin (0.025% gel) for efficacy and side effects. Adapalene produced significantly greater lesion reduction than tretinoin and caused less local skin irritation (21).

Adapalene shares with other retinoids the adverse effect, in certain patients, of an inflammatory acne flare toward the end of the first month of therapy. This risk can be reduced by introducing adapalene or tretinoin gradually. The retinoid is generally applied 2–3 times per week initially, and increasing to nightly use over a period of about 2 months. Oral or topical antibiotics are often combined with retinoid therapy, due to their ability to inhibit the inflammatory process.

Tazarotene, a synthetic acetylenic retinoid, was introduced in 1997 as a gel to treat psoriasis. After topical application, it is rapidly converted to its active metabolite, tazarotenic acid. Two large clinical studies found tazarotene 0.1% gel to be more effective than vehicle in the treatment of acne (22), but erythema and irritation were common side effects. A tazarotene cream is now available as well. A new method of acne treatment, called short-contact tazarotene therapy, has been developed by the author. This method involves applications once or twice daily of tazarotene (0.1%) gel for 2–5 minutes per application, followed by thorough rinsing with warm water. In a pilot study of this method, 20 patients with facial acne applied open-label tazarotene 0.1% gel using the short-contact method. Fourteen patients (70%) achieved at least 50% reduction in acne lesions within 12 weeks of therapy (see

Figure) (23). There was no control group in this early study, but subsequent vehicle-controlled clinical trials support the efficacy of this novel method (22).

### Azelaic Acid

Azelaic acid is a naturally occurring dicarboxylic acid. Available in a 20% cream formulation, it has been demonstrated to prevent follicular hyperkeratosis, thereby inhibiting comedogenesis (14). It also has antimicrobial activity, being bacteriostatic against *P. acnes* and *Staphylococcus epidermidis* (24). Furthermore, it does not appear to induce resistant *P. acnes* (25).

Clinically, azelaic acid 20% cream has been shown to have efficacy comparable to other topical medications (25). It is associated with a low rate of adverse effects, the most common being local itching and burning sensations.

### Alpha-Hydroxy Acids

AHAs are carboxylic acids that contain a hydroxy group on their second (alpha) carbon. These occur naturally in sugar cane, fruits, and milk products. The most useful AHAs in dermatological practice are glycolic acid, lactic acid, and gluconic acid (gluconolactone).

Since the 1970s, it has been known that AHAs facilitate desquamation of the stratum corneum (26). This finding has led to the clinical use of AHAs in the treatment of comedonal acne. Because these compounds are not patent-protected drugs under strict FDA control, large well-controlled trials are lacking. However, there is evidence suggesting acne improvement with AHAs, especially glycolic acid and gluconolactone (27, 28).



**Figure.** (A) A 17-year-old patient, previously untreated for acne. (B) After 7 weeks of short-contact tazarotene therapy (23).

AHAs currently available for acne treatment consist mainly of 5–10% glycolic acid in water-based lotions or hydroalcoholic solutions. Peeling agents containing 30–50% glycolic acid may be used in the office setting (28).

Lower concentrations of AHAs derive their therapeutic usefulness in part due to the lower likelihood of causing skin irritation. As non-prescription products, they have found their way into the treatment of mild acne, particularly in pre-adolescents and adult females.

### Inflammatory Acne

Since the primary lesion of all forms of acne is the comedo, a majority of acne patients can benefit by using keratolytic agents. In addition, when the predominant lesion type is the inflammatory papule or pustule, the traditional mainstays of treatment are topical and systemic antibiotics.

“Combination therapy” for acne is generally defined as ongoing treatment with two or more agents applied at different times. Commonly, a topical antibiotic is applied in the morning and a keratolytic agent is applied at bedtime. Because antibiotic-resistant *P. acnes* and staphylococci are well documented (29, 30), a better regimen might be twice-daily antibiotic followed by a keratolytic agent at bedtime. If two agents are applied at the same time, care must be taken to ensure that the two are compatible and that they are not thereby diluted to ineffective strengths. For example, tretinoin is inactivated by benzoyl peroxide, while adapalene and tazarotene are not.

### Benzoyl Peroxide

Benzoyl peroxide is a potent bactericidal agent that is widely available in prescription and non-prescription acne products, including gels, lotions and cleansers. In concentrations of 2.5–10%, it effectively reduces *P. acnes* and free fatty acids in sebum (31). There is evidence that it reduces comedones (14, 32), in addition to improving inflammatory acne (33).

Common adverse effects include dry skin and bleaching of the skin and fabrics. Occasionally, true contact allergy occurs. Recent concerns that benzoyl peroxide enhances carcinogenesis in laboratory animals (34) are thought to be of little relevance to humans by the scientific community (35).

### Topical Antibiotics

The topical antibiotics clindamycin and erythromycin have been available as hydroalcoholic solutions for about two decades. Newer formulations intended to reduce skin irritation include hydrophilic gels and lotions. The 1990s have seen an increase in the popularity of the pledget application system, which is often more convenient than the traditional applicator bottle.

These agents have been shown to reduce colonization of *P. acnes*, and they may also possess direct anti-inflammatory effects via suppression of neutrophil chemotaxis (36, 37).

A clinical study showed that two different topical solutions, one containing 1.5% erythromycin and the other containing 1% clindamycin, were therapeutically equivalent for acne (37). Further, in a double-blind clinical trial, therapy with clindamycin 1% solution was found to be as effective as oral tetracycline 250 mg twice daily (38).

Two fixed combination gels, the first containing erythromycin 3% with benzoyl peroxide 5% and the second containing clindamycin 1% with benzoyl peroxide 5%, have been found to be superior to their individual components for acne treatment (32, 39, 40). An added advantage of these combinations may be a reduction in drug-resistant *P. acnes* (29). Erythromycin is also available as a 2% solution with zinc, a suppressor of inflammation. A recent study suggests that zinc may act mainly as an inhibitor to penetration, leaving the antibiotic on the skin surface longer (41). The clinical correlate of this finding is unclear.

Other topical antibiotics that are useful in acne treatment include metronidazole, elemental sulfur and sulfur compounds. These may act mainly as direct inhibitors of inflammation; they are generally considered to be more useful in treating acne rosacea, a condition with early inflammation, than true acne, which starts with comedogenesis.

### Systemic Antibiotics

There has been little change in systemic antibiotic therapy for acne in recent years. Oral drugs are indicated for moderate-to-severe forms of acne, particularly those with a potential for scarring.

Effective systemic therapies for acne include: tetracycline and its relatives minocycline and doxycycline; erythromycin; azithromycin;

and trimethoprim alone or in combination with sulfamethoxazole (42). Traditionally, systemic antibiotic treatment has been initiated in the modest-to-low-dose range, which is then tapered over a period of weeks to months. It may be time to reconsider this strategy, in recognition of the increase in antibiotic-resistant bacteria, which occurs not only in acne patients, but also in their household contacts (29). A suggested alternative is full-dose antibiotic treatment for 2–3 weeks, given at several-month intervals, for acne flares.

Each oral medication has known side effects, the most notable in this category being: phototoxicity from the tetracycline group, especially doxycycline; vertigo-like dizziness from minocycline; gastrointestinal distress from erythromycin; and drug eruptions, including Stephens-Johnson syndrome, from trimethoprim-sulfamethoxazole. In addition, all oral antibiotics predispose to *Candida* infections, particularly vaginitis.

A recent study of the safety of the tetracycline-related antibiotics showed minocycline to have a greater tendency than tetracycline and doxycycline to cause rare adverse effects, including hypersensitivity reactions, serum-sickness-like reactions, drug-induced lupus, and single organ failure (43). While minocycline is generally considered safe for long-term use (44), these rare but serious reactions, as well as its higher cost, must be taken into account.

### Hormonal Therapy

Numerous studies have shown a direct correlation between serum androgen levels and acne (45, 46). Androgens increase sebaceous gland activity and may also cause hyperkeratosis of the pilosebaceous gland (47). It has also been hypothesized that sebaceous glands of acne-prone individuals are hyperresponsive to normal serum androgen levels (48).

While oral contraceptives have been used successfully in acne treatment for decades, this mode of therapy for female patients made a recent breakthrough. For the first time, in 1997, the FDA approved a triphasic, combination oral contraceptive (OC), which contains norgestimate 0.215 mg and ethinyl estradiol 0.035 mg, to be used specifically for acne treatment. This decision followed a large, multicenter study which showed that this OC reduced acne lesion counts by more than 50% in female subjects, compared with lesion reductions of about 26% in controls (49). The progestin in this combi-

nation has low intrinsic androgenicity and minimal antiestrogenic effects (50).

It should be noted that acne improvement during treatment with norgestimate/ethinyl estradiol might take 3–4 months to become apparent (49). The principal adverse effect noted in this study was nausea. As expected, OC treatment was protective against pregnancy and appeared to alleviate dysmenorrhea, which was more common in the control group. The chief limitation of anti-androgen therapy for acne is the obvious one: it cannot be used with male patients.

An alternative drug for treating hormonal acne in women is spironolactone (51), which can be combined with OC therapy. Other anti-androgenic therapies that may prove useful in the future include cyproterone acetate, flutamide, finasteride, and gonadotropin-releasing hormone agonists (52, 53).

### Nodulocystic Acne

All of the treatments mentioned previously can be used with some success in severe, nodulocystic acne. Particularly useful are oral antibiotics combined with topical keratolytic agents, as well as hormonal therapy in women. While oral and intralesional corticosteroids are useful as temporary measures to help control severe outbreaks (54), chronic corticosteroid use is contraindicated in acne.

### Isotretinoin

After two decades of retinoid research, isotretinoin (13-cis-retinoic acid) remains the treatment of choice for recalcitrant nodulocystic acne and the more severe variant, acne conglobata (55). Isotretinoin causes de-differentiation of the sebaceous gland, suppressing sebum production to pre-adolescent levels (56). As with other retinoids, it also promotes shedding of keratinocytes. In addition, colonization with *P. acnes* subsides, due to disappearance of sebum.

Isotretinoin's clinical effect on acne is dramatic, often reducing lesion counts by 90% or more within three months. Its results are prolonged, with one 20-week course producing significant improvement for 3 years or longer in about 80% of patients (57).

The usual dosage range of isotretinoin is 0.5–2.0 mg/kg/day. Studies have shown doses as low as 0.1 mg/kg/day to be effective, but acne relapse rates are high, approaching 50%, at this dose (58). As a predictor of the final outcome, researchers have observed that the 20-

week cumulative dose is more important than the daily dose. In 1997, a consensus regarding isotretinoin dosage was reached among international acne experts (59). Their guidelines recommend a cumulative dose of 120 mg per kilogram of body weight over a single 20-week course of therapy, using the original oral formulation of isotretinoin. Currently, an ultramicrocrystallized form of oral isotretinoin is being introduced for the purpose of more efficient absorption of the active ingredient. It is unclear how this new product may impact dosing guidelines.

Because isotretinoin has a half-life of 10–20 hours, 24-hour dosing intervals are adequate, but twice-daily dosing may reduce side effects.

Although 15–20 weeks is the standard course of isotretinoin, practitioners who follow cumulative dosing guidelines may choose to vary the length of treatment slightly. FDA guidelines, however, still include an 8-week drug-free period following 20 weeks of isotretinoin.

Neither federal guidelines nor common sense supports the concept of “pulse-dosing” with isotretinoin. It is likely that the risk of teratogenicity, isotretinoin’s most serious side effect (60), would increase when drug treatment is prolonged, interrupted or inadequately monitored. In a recent study of intermittent dosing with isotretinoin for one week each month over 6 months, resolution of acne was impressive, about 90%, but the 12-month relapse rate was close to 40% (61).

Adverse effects from isotretinoin are seen in virtually 100% of its users but generally subside one to three weeks after cessation of therapy. Dryness of the skin and mucous membranes, and chapped lips (retinoid cheilitis) are universal at therapeutic doses. Patches of eczema (retinoid dermatitis) occur commonly, typically on the dorsal hand and forearm. These complaints are managed with moisturizers, greasy topical corticosteroids, and dosage adjustment, if necessary. Skin fragility and susceptibility to sunburn are frequently reported. Dry eyes, nosebleeds, hair shedding, myalgias and arthralgias are not uncommon.

Recently, several cases of psychological depression and even suicide have been reported among patients taking isotretinoin (62). Paradoxically, previous studies had shown an improvement in well-being and self-esteem (63). Whether isotretinoin plays a causal role with regard to these symptoms is unclear, as a recent large, population-based study failed to show an increased risk of depression in isotretinoin users compared with other acne patients (64).

Patients on isotretinoin may experience a temporary flare-up of acne after 2–4 weeks of therapy. As is the case with topical retinoids, gradual introduction of the drug, along with patience, usually leads to a favorable outcome. A rare but troubling event that may occur during isotretinoin therapy is the onset of acne fulminans (65). This condition is a painful, severe exacerbation of cystic acne with exuberant granulation tissue and scarring. Acne fulminans can be managed with variable success by temporarily decreasing the isotretinoin dose and treating concurrently with a short course of systemic corticosteroid (66). Dapsone may also be effective (65).

Tetracycline derivatives and vitamin preparations containing vitamin A should be avoided during isotretinoin therapy, since these medications may increase the risk of pseudotumor cerebri (44), a rare side effect of isotretinoin.

The most notable systemic problems with isotretinoin are its teratogenicity and its effect on serum lipids. The former cannot be overemphasized: the risk of birth defects mandates careful patient selection, contraceptive counseling, and strict monitoring of women who may become pregnant. Isotretinoin is not mutagenic, and federal guidelines suggest that pregnancy is safe one month after drug cessation. Patients may not donate blood during isotretinoin therapy due to its teratogenic potential. Two negative pregnancy tests are now required prior to initiation of isotretinoin therapy, and monthly testing is mandatory for sexually active females during treatment.

Serum lipid and lipoprotein alterations are common, with elevation of triglycerides being reported most frequently (67). Mean triglyceride levels have been shown to increase by about 50% within 2–3 months on the drug, and cholesterol by about 15%. Overweight patients have an increased risk of isotretinoin-induced hypertriglyceridemia. Blood work, including fasting triglyceride and cholesterol levels, should be performed at baseline and at 2–4 week intervals during isotretinoin therapy (56).

Isotretinoin has been linked with premature closure of the epiphyses of long bones in laboratory animals (63). For this reason, some physicians prefer to reserve its use for patients past their growth spurt. A baseline serum alkaline phosphatase level is often helpful to assess the level of adolescent bone growth.

Some degree of acne relapse after isotretinoin treatment occurs in a significant number of cases, perhaps as many as 60%

within three years (57). Patients at particular risk for recurrence are adolescents under the age of 18, women with hormonal acne (68), and patients whose cumulative dose is less than 100 mg per kilogram (57). Relapses are usually minor and can be managed with conservative topical therapy. About 20% of patients have acne relapses severe enough to warrant retreatment with isotretinoin after a drug-free interval of at least eight weeks.

### Discussion and Summary

With so many acne treatments available, there are four principal reasons why this disorder remains a common affliction. First, not everyone pursues medical treatment for acne. Second, the health practitioner might not select the optimum therapy for a given patient. Third, the patient may not understand or comply with the treatment regimen. And finally, the perfect drug for acne — one that is safe and efficacious for all varieties of the disorder — does not exist.

Physicians carry the responsibility of educating the public, as well as health insurance carriers, on the need for acne treatment. Acne is a physically and emotionally debilitating disorder that requires medical care, regardless of cost-cutting trends in our health-care system.

While the physician must choose wisely from the array of treatment options, dermatology care remains as much an art as a science. Effective physician-patient communication is crucial if any regimen is to provide its maximum benefit. Patients must be educated to apply topical therapies to nonlesional skin as well as to blemishes, and to understand that all acne medications are essentially prophylactic. They should also be taught the importance of continuing treatment when the condition is at its best. Using topical and oral antibiotics in an "ad lib" fashion may lead to resistant bacteria and chronic treatment failure.

Finally, certain conclusions can be made about current medications, imperfect as they may be. Topical therapy should be relied upon when possible, to minimize side effects. Combination therapy with a keratolytic agent and a topical antibiotic is a rational approach. While oral antibiotics have an important role, care must be taken to avoid their haphazard use.

Isotretinoin has revolutionized acne therapy. Its use requires expert patient selection, education, and monitoring. Until the next generation of therapeutic options is realized, isotretinoin remains the choice for difficult cystic acne.

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